

CLAIMS

What is claimed is:

1. A treatment regimen for a mammal with neoplastic disease, comprising the steps of administering a therapeutic dose of a gallium compound and administering a therapeutic dose of at least one nonchemotherapeutic anticancer agent (NCAA).
2. The method of claim 1 wherein the gallium compound and NCAA are administered simultaneously.
3. The method of claim 1 wherein the gallium compound and NCAA are administered separately.
4. The method of claim 3 wherein administration of the gallium compound and NCAA are separated by a selected time interval.
5. The method of claim 1 wherein the gallium compound is gallium nitrate.
6. The method of claim 1 wherein the NCAA is an antibody.
7. The method of claim 1 wherein the NCAA is a small molecule.
8. The method of claim 6 or 7 wherein the gallium compound is gallium nitrate.
9. The method of claim 1 wherein the NCAA is at least one compound selected from the group consisting of an antibody, an antisense molecule, an anti-telomerase agent, a biologic response modifier, a bisphosphonate, a cytotoxic fusion protein, an immunomodulatory agent, an immunostimulatory agent, a molecular inhibitor, a proteasome inhibitor, a protein kinase inhibitor, a retinoid, a transcription factor and an arsenic compound.
10. The method of claim 9 wherein the gallium compound is gallium nitrate.
11. The method of claim 10 wherein the dose of gallium nitrate is about 100 mg/m²/d to about 400 mg/m²/d.

12. The method of claim 11 wherein the dose of gallium nitrate is about 250 mg/m²/d to about 350 mg/m²/d.
13. The method of claim 12 wherein the dose of gallium nitrate is about 300 mg/m²/d.
14. The method of claim 11 wherein the gallium nitrate is administered over about 3 days to about 8 days.
15. The method of claim 14 wherein the gallium nitrate is administered over about 5 days to about 7 days.
16. The method of claim 15 wherein the gallium nitrate is administered over about 7 days.
17. The method of claim 9 wherein the NCAA is at least one antibody, selected from the group consisting of a monoclonal antibody, a genetically engineered antibody, a bispecific antibody, an antibody fragment, a single-chain antibody, an scFv fragment, an Fab fragment, an F(ab)' fragment, and an (Fab)'₂ fragment.
18. The method of claim 17 wherein the gallium compound is gallium nitrate.
19. The method of claim 17 wherein the antibody is selected from the group consisting of a humanized antibody and a chimeric antibody.
20. The method of claim 17 wherein the antibody is selected from the group consisting of alemtuzumab, cetuximab, epratuzumab (LL2, hLL2), gemtuzumab ozogamicin, ibritumomab tiuxetan, rituximab, tositumomab, trastuzumab, and anti-CD19/anti-CD3 single-chain bispecific antibody (bscCD19xCD3).
21. The method of claim 20 wherein the antibody is rituximab.
22. The method of claim 21 wherein the dose of rituximab is about 250 mg/m²/d to about 425 mg/m²/d.
23. The method of claim 21 wherein the dose of rituximab is about 325 mg/m²/d to about 400 mg/m²/d.

24. The method of claim 21 wherein the dose of rituximab is about $375 \text{ mg/m}^2/\text{d}$.
25. The method of claim 22 wherein the rituximab is administered weekly to about once monthly.
26. The method of claim 22 wherein the rituximab is administered weekly.
27. The method of claim 20 wherein the gallium compound is gallium nitrate.
28. The method of claim 20 wherein the antibody is alemtuzumab.
29. The method of claim 28 wherein the dose of alemtuzumab is about 3 mg/d to about 30 mg/d.
30. The method of claim 28 wherein the dose of alemtuzumab is less than about 30 mg/d.
31. The method of claim 28 wherein the dose of alemtuzumab is about 30 mg/d.
32. The method of claim 31 wherein the alemtuzumab is administered about three times weekly.
33. The method of claim 32 wherein the duration of administration of alemtuzumab is up to about 12 weeks.
34. The method of claim 20 wherein the antibody is cetuximab.
35. The method of claim 34 wherein the dose of cetuximab is between about 250 mg/m^2 to about 400 mg/m^2 .
36. The method of claim 34 wherein an initial dose of cetuximab is about 400 mg/m^2 and subsequent maintenance doses are about 250 mg/m^2 .
37. The method of claim 20 wherein the antibody is epratuzumab (LL2, hLL2).
38. The method of claim 37 wherein the dose of epratuzumab is about 360 mg/m^2 to about 480 mg/m^2 .

39. The method of claim 37 wherein the dose of epratuzumab is about 380 mg/m² to about 460 mg/m².
40. The method of claim 37 wherein the dose of epratuzumab is about 400 mg/m² to about 440 mg/m².
41. The method of claim 38 wherein the dose of epratuzumab is administered weekly.
42. The method of claim 20 wherein the antibody is gemtuzumab ozogamicin.
43. The method of claim 42 wherein the dose of gemtuzumab ozogamicin is about 7 mg/m² to about 11 mg/m².
44. The method of claim 42 wherein the dose of gemtuzumab ozogamicin is about 8 mg/m² to about 10 mg/m².
45. The method of claim 42 wherein the dose of gemtuzumab ozogamicin is about 9 mg/m².
46. The method of claim 43 wherein the gemtuzumab ozogamicin is administered over about 2 hours.
47. The method of claim 46 wherein a treatment consists of a total of two doses of gemtuzumab ozogamicin administered about 14 days apart.
48. The method of claim 20 wherein a first antibody is rituximab and a second antibody is ibritumomab tiuxetan and the first and second antibodies are administered sequentially.
49. The method of claim 48 wherein an initial dose of the rituximab is about 250 mg/m².
50. The method of claim 49 wherein a dose of rituximab is followed by a dose of about 5 mCi of In¹¹¹-labeled ibritumomab tiuxetan.

51. The method of claim 50 wherein the In¹¹¹-labeled ibritumomab tiuxetan is administered over a period of about 10 minutes.
52. The method of claim 51 wherein the In¹¹¹-labeled ibritumomab tiuxetan is followed by a second dose of rituximab.
53. The method of claim 52 wherein the second dose of rituximab is about 250 mg/m².
54. The method of claim 53 wherein the second dose of rituximab is followed by a dose of about 0.3 mCi/kg (11.1 MBq/kg) to about 0.4 mCi/kg (14.8 MBq/kg) of Y⁹⁰-labeled ibritumomab tiuxetan.
55. The method of claim 54 wherein the Y⁹⁰-labeled ibritumomab tiuxetan is administered over a period of about 10 minutes.
56. The method of claim 20 wherein the antibody is tositumomab.
57. The method of claim 56 wherein the dose of tositumomab is about 450 mg.
58. The method of claim 57 wherein the dose of tositumomab is administered over about one hour.
59. The method of claim 56 wherein an initial dose of tositumomab is administered and thereafter a second dose of about 35 mg of tositumomab radiolabeled with about 5 mCi of iodine¹³¹ is administered.
60. The method of claim 59 wherein the dose of radiolabeled tositumomab is administered over about thirty minutes.
61. The method of claim 20 wherein the antibody is trastuzumab.
62. The method of claim 61 wherein the trastuzumab is administered once weekly.
63. The method of claim 62 wherein an initial dose of trastuzumab is about 3 mg/kg to about 5 mg/kg.

64. The method of claim 62 wherein an initial dose of trastazumab is about 3.5 mg/kg to about 4.5 mg/kg.
65. The method of claim 64 wherein the initial dose of trastazumab is about 4 mg/kg.
66. The method of claim 63 wherein the initial dose of trastazumab is administered over about 90 minutes.
67. The method of claim 62 wherein a weekly dose of trastuzumab is about 1 mg/kg to about 3 mg/kg.
68. The method of claim 62 wherein a weekly dose of trastuzumab is about 1.5 mg/kg to about 2.5 mg/kg.
69. The method of claim 62 wherein a weekly dose of trastuzumab is about 2 mg/kg.
70. The method of claim 62 wherein a weekly dose of trastuzumab is administered over about 30 minutes..
71. The method of claim 20 wherein the antibody is anti-CD19/anti-CD3 single-chain bispecific antibody (bscCD19xCD3).
72. The method of claim 9 wherein the NCAA is an antisense molecule.
73. The method of claim 72 wherein the antisense molecule is oblimersen sodium :
74. The method of claim 73 wherein a dose of oblimersen sodium is about 0.01 mg/kg/d to about 50 mg/kg/d.
75. The method of claim 73 wherein a dose of oblimersen sodium is about 4 mg/kg/d to about 9 mg/kg/d.
76. The method of claim 73 wherein a dose of oblimersen sodium is about 5 mg/kg/d to about 7 mg/kg/d.
77. The method of claim 74 wherein the dose of oblimersen sodium is administered over about 2 days to about 13 days.

78. The method of claim 74 wherein the dose of oblimersen sodium is administered over about 3 days to about 9 days.
79. The method of claim 74 wherein the dose of oblimersen sodium is administered over about 4 days to about 8 days.
80. The method of claim 74 wherein the dose of oblimersen sodium is administered over about 5 days.
81. The method of claim 9 wherein the NCAA is an anti-telomerase agent.
82. The method of claim 81 wherein the anti-telomerase agent is selected from the group consisting of an antisense molecule, a small molecule and an oligomer.
83. The method of claim 82 wherein the anti-telomerase agent is GRN163.
84. The method of claim 1 wherein the NCAA is an aptamer.
85. The method of claim 9 wherein the NCAA is at least one biologic response modifier, selected from the group consisting of interleukin-2 (IL-2, aldesleukin), interleukin-11 (IL-11), interleukin-12 (IL-12), and interferon-alpha2a (IFN- α 2a).
86. The method of claim 85 wherein the biologic response modifier is aldesleukin.
87. The method of claim 86 wherein the dose of aldesleukin is about 500,000 IU/kg to about 700,000 IU/kg.
88. The method of claim 86 wherein the dose of aldesleukin is about 550,000 IU/kg to about 650,000 IU/kg.
89. The method of claim 86 wherein the dose of aldesleukin is about 600,000 IU/kg.
90. The method of claim 87 wherein the aldesleukin is administered about daily for about 5 days.

91. The method of claim 87 wherein the aldesleukin is administered in two treatment cycles separated by about nine days.
92. The method of claim 9 wherein the NCAA is a bisphosphonate.
93. The method of claim 9 wherein the NCAA is a cytotoxic fusion protein.
94. The method of claim 93 wherein the cytotoxic fusion protein is denileukin diftitox.
95. The method of claim 94 wherein the dose of denileukin diftitox is about 8 µg/kg/d to about 10 µg/kg/d.
96. The method of claim 94 wherein the dose of denileukin diftitox is about 16 µg/kg/d to about 20 µg/kg/d.
97. The method of claim 94 wherein the dose of denileukin diftitox is about 9 µg/kg/d to about 18 µg/kg/d
98. The method of any of claims 95, 96, and 97 wherein 1 to about 8 cycles of denileukin diftitox are administered.
99. The method of any of claim 95, 96, and 97 wherein 2 to about 6 cycles of denileukin diftitox are administered.
100. The method of any of claims 95, 96, and 97 wherein about 4 cycles of denileukin diftitox are administered
101. The method of claim 9 wherein the NCAA is an immunomodulatory agent.
102. The method of claim 101 wherein the immunomodulatory agent is thalidomide.
103. The method of claim 102 wherein the dose of thalidomide is about 50 mg/d to about 800 mg/d.
104. The method of claim 102 wherein the dose of thalidomide is about 50 mg/d to about 300 mg/d.

105. The method of claim 102 wherein the dose of thalidomide is about 200 mg/d to about 400 mg/d.
106. The method of claim 103 wherein the dose of thalidomide is administered once daily.
107. The method of claim 9 wherein the NCAA is an immunostimulatory agent.
108. The method of claim 107 wherein the immunostimulatory agent is CpG oligodeoxynucleotide.
109. The method of claim 1 wherein the NCAA is a molecular decoy.
110. The method of claim 9 wherein the NCAA is a molecular inhibitor.
111. The method of claim 110 wherein the molecular inhibitor is P-glycoprotein inhibitor.
112. The method of claim 111 wherein a dose of P-glycoprotein inhibitor is about 5 mg/kg.
113. The method of claim 110 wherein a treatment cycle of the P-glycoprotein inhibitor comprises about 12 doses administered over two to three days.
114. The method of claim 113 wherein the treatment cycle is repeated weekly to about once monthly.
115. The method of claim 9 wherein the NCAA is a proteasome inhibitor.
116. The method of claim 115 wherein the proteasome inhibitor is bortezomib.
117. The method of claim 116 wherein the dose of bortezomib is about 1.0 mg/m² to about 1.3 mg/m².
118. The method of claim 116 wherein the dose of bortezomib is about 1.3mg/m².

119. The method of claim 117 wherein the bortezomib is administered on day 1, and thereafter on about day 4, about day 8, and about day 11 of a 21-day cycle for up to about eight cycles.
120. The method of claim 9 wherein the protein kinase inhibitor is selected from the group consisting of a protein tyrosine kinase inhibitor and a protein kinase C inhibitor.
121. The method of claim 120 wherein the protein tyrosine kinase inhibitor is imatinib mesylate.
122. The method of claim 121 wherein the dose of imatinib mesylate is about 300 mg/d to about 800 mg/d.
123. The method of claim 121 wherein the dose of imatinib mesylate is about 500 mg/d to about 700 mg/d.
124. The method of claim 121 wherein the dose of imatinib mesylate is about 600 mg/d.
125. The method of claim 121 wherein the dose of imatinib mesylate is about 400 mg/d.
126. The method of claim 122 wherein the dose of imatinib mesylate is administered once daily.
127. The method of claim 1 wherein the NCAA is gefitinib.
128. The method of claim 127 wherein the dose of gefitinib is about 250 mg/d.
129. The method of claim 128 wherein the dose of gefitinib is administered about once daily.
130. The method of claim 120 wherein the protein kinase C inhibitor is ruboxistaurin mesylate.
131. The method of claim 130 wherein the dose of ruboxistaurin mesylate is about 32 mg to about 64 mg.

132. The method of claim 130 wherein the dose of ruboxistaurin mesylate is about 32 mg.
133. The method of claim 9 wherein the NCAA is a retinoid.
134. The method of claim 133 wherein the retinoid is selected from the group consisting of bexarotene and tretinooin.
135. The method of claim 134 wherein the retinoid is bexarotene.
136. The method of claim 135 wherein the dose of bexarotene is about 100 mg/m²/d to about 1,000 mg/m²/d.
137. The method of claim 135 wherein the dose of bexarotene is about 300 mg/m²/d to about 400 mg/m²/d.
138. The method of claim 135 wherein the dose of bexarotene is about 300 mg/m²/d.
139. The method of claim 134 wherein the retinoid is tretinooin.
140. The method of claim 139 wherein the dose of tretinooin is about 40 mg/m²/d to about 50 mg/m²/d.
141. The method of claim 139 wherein the dose of tretinooin is about 45 mg/m²/d.
142. The method of claim 141 wherein the dose of tretinooin is administered in two separate portions.
143. The method of claim 9 wherein the NCAA is a transcription factor.
144. The method of claim 143 wherein the transcription factor is nuclear factor-kappa B (NF-κB).
145. The method of claim 9 wherein the NCAA is an arsenic compound.
146. The method of claim 145 wherein the arsenic compound is arsenic trioxide.

147. The method of claim 146 wherein the dose of arsenic trioxide is about 0.15 mg/kg daily.
148. The method of claim 147 wherein the dose of arsenic trioxide is administered for about 25 doses over a period up to about 5 weeks.
149. The method of claim 1 wherein the NCAA is a compound directed to a target molecule selected from the group consisting of CD52 antigen, epidermal growth factor receptor, CD22 receptor, CD33 antigen, CD20 antigen, HER-2 receptor, CD19 antigen and CD3 antigen.
150. The method of claim 1 wherein the gallium compounds, NCAA compounds and formulations thereof, are adapted for use in the manufacture of drugs for administration to patients having neoplastic disease.